IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Dale B. Schenk

Application No.: 09/724,953

Filed: November 28, 2000

For: PREVENTION AND TREATMENT OF AMYLOIDOGENIC DISEASE

Examiner: Christopher J. Nichols

Art Unit: 1647

DECLARATION UNDER 37 C.F.R. § 1.132 OF MARTIN KOLLER, M.D., M.P.H.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Martin Koller, M.D., M.P.H., state as follows.

(1) My current position is Vice President, Clinical Development – North America at Elan Pharmaceuticals, the parent company of Neuralab, Inc, which is the assignee of the above-captioned application. I have designed and conducted many clinical trials and have experience at interpreting the results of clinical trials. A copy of my curriculum vitae is attached.

(2) A phase I human clinical trial (Study AN1792(QS-21)-102, henceforth designated as Study 102), was conducted in which AN1792 (42 amino acid synthetic formulation of Aβ) plus the adjuvant QS-21 was administered to patients suffering from Alzheimer's disease (AD) in comparison to a placebo control group (adjuvant alone). Study 102 was an exploratory, randomized, multi-center, double-blind, multi-dose, dose-escalation, adjuvant-controlled, safety, tolerability and immunogenicity study in patients with mild to moderate AD in which up to 8 injections of study drug were administered to patients over 18 months. The study was designed to assess 4 dose groups of AN1792(QS-21) with 20 patients per group, randomized to active vs placebo in a 4 to 1 ratio resulting in a total of 64 active and 16 control patients within the study.

(3) The functional disability of patients in this trial was assessed before treatment with Aβ (baseline) and at intervals thereafter. The clinical outcome measure used to measure functional disability was the Disability Assessment for Dementia (DAD) scale. The

DAD scale is an instrument developed and validated to measure the functional disability of patients with AD (Gelinas et al., Am. J. Occup. Ther. 53, 471-481 (1999)). Caregivers answered questions about the patients' ability to perform independently both instrumental and basic activities of daily living that had been attempted in the preceding two weeks. The proportion of DAD activities successfully completed out of those attempted was then calculated and reported as a percentage.

(4) The results from patients administered placebo versus patients administered Aβ are displayed in Figure 1 and listed in Table 1. The patients treated with Aβ were classified based on antibody titer ("Responders", "Sub-Threshold" titers, and "No Antibody" titers). The "Responders" were patients who had a titer that was 1:1,000 or greater 4 weeks after any injection or a titer that was 1:5,000 or greater at any time point after baseline. The "Sub-Threshold" titer responders are patients who had titers between 101-999 four weeks after any injection. The "No Antibody" titer patients are patients who had a titer that was 1:100 (the functional limit of the assay) four weeks after any injection.

(5) The average DAD score for all patients administered active versus placebo are listed in Table 1. A decline in score over time indicates a decline in functional abilities of the patients. The significant differences in the reduction of the decline noted in the treated patients as compared with the placebo patients is an indication that the treatment resulted in a beneficial effect by preserving functional abilities (e.g., the placebo group decline was greater than the decline seen the treated patients).

(6) The magnitude of the observed DAD effect in individual patients did not correlate strongly with the different magnitudes of antibody titer in the treated groups.

(7) An additional, exploratory phase IIa clinical trial (Study AN1792(QS-21)-201, henceforth Study 201) has been conducted in which AN1792(QS-21) was administered to human patients in comparison to placebo (normal saline). Study 201 was a multi-center, randomized, double-blind, multi-dose, placebo-controlled, safety, tolerability, and pilot efficacy study in patients with mild to moderate AD wherein 2 dose groups were studied (AN1792(QS-21) versus placebo with planned dosing of up to 6 injections to be administered over 12 months). The trial was halted after the vast majority of patients in the trial received only 2 doses of study

drug due to reports of encephalitis in a small number of patients (as has been reported in the press and scientific literature). Although study drug administration was halted, patients were followed for up to 12 months, and change from baseline to Month 12 DAD scores were still calculated. In this truncated trial, differences between the treated patients versus the placebo group did not reach statistical significance. Since dosing and the observation period for Study 201 had to be terminated early due to the occurrence of encephalitis, the DAD results from these two trials (Studies 102 and 201) are not comparable. In Study 201, patients were given fewer doses of study drug and the DAD scores were assessed over a shorter time period than in Study 102. Even with the greater number of dosages administered in Study 102, the change from baseline to Week 64 DAD scores failed to reach statistical significance (significance was defined as p-value < 0.05). The DAD data for studies 102 and 201 are summarized in Figure 2.

(8) In my opinion, the results from Study 102 described above provide evidence that administration of AN1792(QS-21) is of benefit in treating patients with Alzheimer's disease.

(9) I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Martin Koller, M.D., M.P.H.

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Figure No. 1: Study AN1792(QS-21)-102

Mean DAD Adjusted Change from Baseline Scores (in percents) by Titer Response

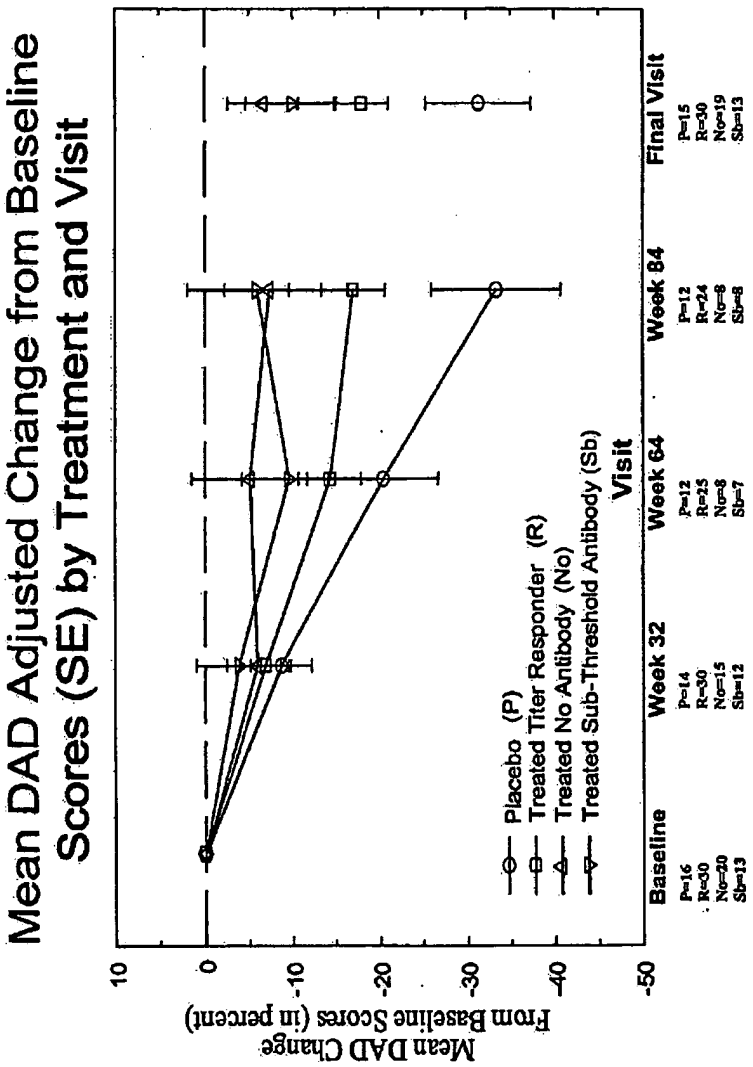
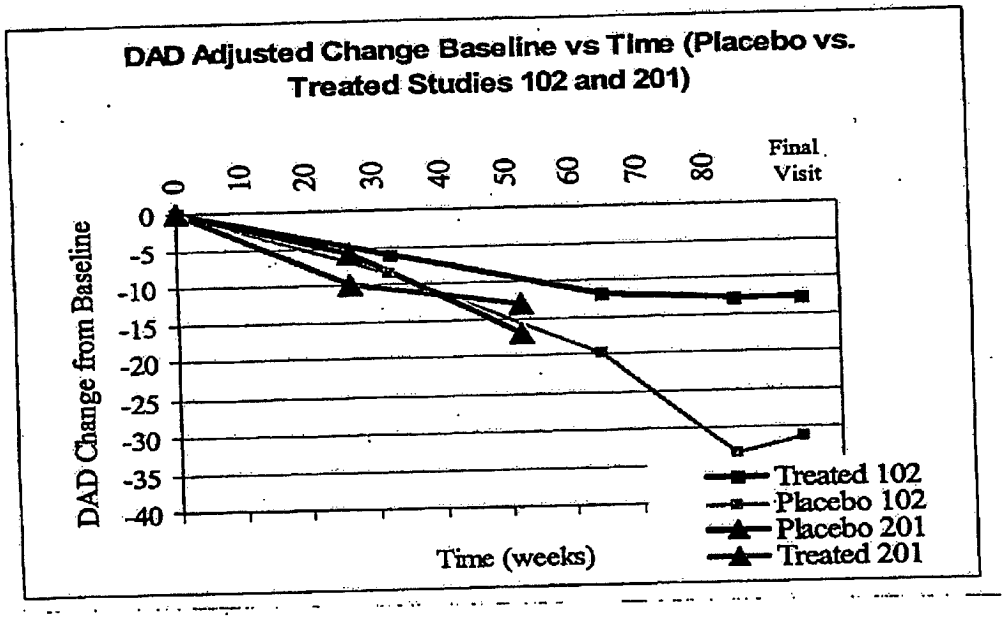


TABLE 1
Total DAD Scores
AN1792 - Protocol 102

FOR slot OTHERS	THERAPY GROUP	NUMBER OF PATIENTS	RAW MEAN SCORE	RAW CHANGE FROM BASELINE	ADJ CHANGE FROM BASELINE	STANDARD ERROR	ADJ MEANS (95% CI.)	DIFF ADJ MEANS (95% CI.) PLACEBO VS OTHERS	P-VALUE PLACEBO VS
BASELINE	1	16	76.56				67.72		
BASELINE	2	30	69.04				67.72		
BASELINE	3	20	64.15				67.72		
BASELINE	4	13	59.27				67.72		
WEEK 32	1	14	68.95	8.69	9.36	3.51	58.67 (50.18,67.16)		
WEEK 32	2	30	62.17	6.86	6.93	2.89	61.10 (55.50,66.71)	2.43 (-7.68,12.55)	0.632
WEEK 32	3	15	58.74	5.99	5.11	3.53	62.92 (54.75,71.09)	4.25 (-7.63,16.14)	0.477
WEEK 32	4	12	54.58	3.86	3.37	4.79	64.67 (55.50,73.83)	6.00 (-6.68,18.68)	0.348
WEEK 64	1	12	60.18	20.48	22.54	6.30	49.38 (38.23,60.53)		
WEEK 64	2	25	57.98	14.35	14.82	3.63	57.09 (49.57,64.62)	7.72 (-5.66,21.10)	0.251
WEEK 64	3	8	57.86	5.12	6.74	6.58	65.17 (51.15,79.19)	15.79 (-2.32,33.91)	0.086
WEEK 64	4	7	56.07	9.60	9.23	5.38	62.69 (48.10,77.28)	13.31 (-5.30,31.92)	0.157
WEEK 84	1	12	45.77	33.36	37.17	7.37	34.59 (22.76,46.42)		
WEEK 84	2	24	56.99	17.00	19.30	3.65	52.46 (44.14,60.78)	17.87 (3.75,32.00)	0.014
WEEK 84	3	8	55.63	7.35	8.28	9.23	63.49 (48.71,78.26)	28.90 (9.88,47.91)	0.004
WEEK 84	4	8	56.91	5.91	3.92	3.71	67.84 (53.38,82.31)	33.25 (14.16,52.35)	0.001
VISIT-FINAL	1	15	45.28	31.38	34.44	6.01	33.61 (23.90,43.31)		
VISIT-FINAL	2	30	51.07	17.97	18.48	3.07	49.56 (42.89,56.23)	15.95 (4.25,27.66)	0.008
VISIT-FINAL	3	19	59.02	6.66	6.19	4.03	61.85 (53.17,70.54)	28.25 (15.19,41.30)	0.000
VISIT-FINAL	4	13	49.38	9.89	7.86	5.21	60.18 (49.73,70.64)	26.58 (12.05,41.10)	0.001

Note: Therapy group decode: 1=Placebo; 2=Treated titer Responders; 3=Treated No Antibody; 4=Treated Sub-Threshold Antibody

Figure No. 2



CURRICULUM VITAE

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EDUCATION:

B. A.	1968 - 1972	Franklin and Marshall College Lancaster, Pennsylvania
M.P.H. - Epidemiology	1972 - 1973	University of Texas School of Public Health Houston, TX
M.D.	1973 - 1977	University of Maryland School of Medicine Baltimore, Maryland
Post-graduate medical: Internship	1977 - 1978	Mount Zion Hospital San Francisco, California
Residency: Psychiatry	1978 - 1979	Mount Zion Hospital San Francisco, California
Residency: Neurology	1980 - 1983	Kaiser Permanente Hospital University of Southern California and Children's Hospital of Los Angeles, Los Angeles, California
Fellowship: Neuromuscular	1983 - 1984	University of Southern California Director: W. King Engel Good Samaritan Hospital Neuromuscular Center

PROFESSIONAL HISTORY:

Elan Pharmaceutical, Inc.	2/03 - present	Vice President - North America
(Athena Neurosciences, Inc.)	6/99 – 1/03	Senior Director, Clinical Research
San Diego, CA	2/94 – 5/99	Director, Clinical Research
Syntex Pharmaceuticals Institute of Cardiovascular & Central Nervous System Palo Alto, CA	11/90 - 2/94	Associate Medical Director

Wyeth-Ayerst Laboratories Clinical Research, CNS Group Radnor, PA	6/90 - 11/90	Associate Medical Director
Northridge Neurological Group Northridge, California	8/84 - 5/90	Neurologist

MEDICAL LICENSES: California: A-32848
Pennsylvania: MD-042008-L

BOARD CERTIFICATION: Diplomate - Specialty of Neurology
American Academy of Psychiatry and Neurology - #29297, 1987

ACADEMIC APPOINTMENTS: Clinical Instructor of Neurology
Department of Neurology
University of Southern California, 1983-1984

PHARMACEUTICAL INDUSTRY EXPERIENCE:

As Vice President of Clinical Development for North America at Elan:

- Leadership and management of a group of approximately 70 clinical development employees (MDs, PhDs, monitors and other administrative staff)
- Responsible for defining and representing clinical strategic and development issues for the Elan organization
- Member of several Elan strategic management committees and teams to set, integrate and achieve overall corporate goals and objectives
- Lead of protocol review initiative to ensure consistent, quality scientific input and review of all Phase I-III projects
- Liaison between European and American clinical development structures to ensure consistent quality for all programs and submissions worldwide
- Integration of new clinical development Standard Operating Procedure processes within the North America Group

Projects and Submissions:

- Multiple IND's filed, 2 NDA's, 1 BLA; multiple phase I-III studies
- Immunotherapeutic Programs for the indication of Alzheimer's disease (4 distinct programs in Alzheimer's disease): AN1792, AAB, ACC, ELN90543
- Beta-secretase program in Alzheimer's disease
- Antegren (monoclonal antibody) for the indication of multiple sclerosis
- Botulinum Toxin Type B (MYOBLOC™, NeuroBloc®) for the indication of cervical dystonia (BLA clinical lead, PI Clinical Negotiation Team Representative, approved 12/00)
- Ciliary Neurotrophic Factor (rhCNTF) for the indication of amyotrophic lateral sclerosis
- DiaStat® for the indication of epilepsy (NDA submission clinical review team)
- Lifarizine for the indication of stroke

Nerve Growth Factor (NGF) for the indication of Alzheimer's disease

Zanaflex® for the indication of spasticity (NDA submission clinical review team)

CDER and CBER experience with 3 applications submitted to FDA (2-NDAs and 1-BLA), multiple IND submissions and regulatory interactions

CLINICAL RESEARCH EXPERIENCE PRIOR TO INDUSTRY:

Immunosuppressive regimens for the treatment of dysimmune dysschwannian neuropathies and inflammatory myopathies

Etiocholanolone and Poly-ICLC for the treatment of dysimmune dysschwannian neuropathies

TRH for the treatment of amyotrophic lateral sclerosis

Dietary manipulations for the treatment of carnitine palmityl transferase deficiency

MANAGEMENT:

Manage a clinical department group (approximately 70 employees) reporting to the President of R&D for several programs (e.g., Alzheimer's disease, multiple sclerosis, epilepsy, pain, Parkinson's disease)

Managed several clinical development programs with multiple staff members and CRO's

Study leader/clinical leader for several projects (national and international project teams)

Consultant and Medical Expert for several CNS project on multiple Joint Venture Teams

Attended several Management Courses (Project Team Leadership, Total Quality Management, Management Training Seminars, Interview and Selection Skills Workshop, Statistical Concepts for Non-Statisticians, etc.)

PAPERS/ABSTRACTS/PUBLICATIONS:

PAPERS:

Cullis P, Moore P, Freeman A, Kumar R, Hammerstad J, Tarsy D, Duane D, Fross R, Massey J, Reich S, Sethi K, Walker F, Hyman N, Swenson M, Lees A, Barnes M, Murray J, Donoghue S, Groves L, Wilmer-Hulme A, Wallace J, and **Koller M.** An Open-Label, Forced Dose-Escalation Safety Study Of Myobloc™ (Botulinum Toxin Type B) In Patients With Cervical Dystonia. *In preparation.*

Sheremata WA, Vollmer TL, Stone LA, Willmer-Hulme AJ and **Koller M.** A safety and pharmacokinetic study of intravenous natalizumab in patients with MS. *Neurology*, 1999;52:1072-1074.

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Brin MF, Lew MF, Adler CH, Comella CL, Factor SA, Jankovic J, O'Brien C, Murray JJ, Wallace JD, Willmer-Hulme A, and **Koller M.** Safety And Efficacy Of Neurobloc™ (Botulinum Toxin Type B) In Type A-Resistant Cervical Dystonia Patients, *Neurology*,1999;53:1431-1438.

Lew MF, Adornato BT, Duane DD, Dykstra DD, Factor SA, Massey JM, Brin MF, Jankovic J , Rodnitzky RL , Singer C, Swenson MR, Tarsy D, Murray JJ, **Koller M** and Wallace JD . Botulinum Toxin Type B (BotB): A Double-Blind, Placebo-Controlled, Safety and Efficacy Study in Cervical Dystonia. *Neurology*, 1997;49(3):701-711.

Truong DD, Cullis PA, O'Brien CF, **Koller M**, Graces A, Villegas T, and Wallace JD: BotB™ (Botulinum Toxin Type B): Evaluation of Safety and Tolerability in Botulinum Toxin Type A-Resistant Cervical Dystonia Patients. *Movement Dis*, 1997;12(5):772-775.

ABSTRACTS:

Cullis PA, Barnes M, Duane D, Chen REW, Freeman A, Fross R, Hammerstad J, Hyman N, Lees A, Massey J, Moore P, Reich S, Sethi K, Swenson M, Tarsy D, Walker F, Murray JJ, Willmer-Hulme A, Donoghue S, Wallace JD, **Koller M**. Safety and Tolerability of Repeat Doses of NeuroBloc™ (Botulinum Toxin Type B) in Patients with Cervical Dystonia: An Open-Label, Dose-Escalation Study. Abstract – International Conference 1999: Basic and Therapeutic Aspects of Botulinum and Tetanus Toxins, Orlando, FL, 1999 (in press).

Factor SA, Adler CA, Brashear A, Brin MF, Comella CL, Dykstra DD, Jankovic J, Lew MF, O'Brien C, Rodnitzky RL, Singer C, Trosch R, Murray JJ, Willmer-Hulme A, Wallace JD, **Koller M**. Safety and Efficacy of NeuroBloc™ (Botulinum Toxin Type B) in Type A Responsive and Type A Resistant Patients with Cervical Dystonia. Abstract – International Conference 1999: Basic and Therapeutic Aspects of Botulinum and Tetanus Toxins, Orlando, FL, 1999 (in press).

Koller M, Wallace JD, Willmer-Hulme A, Chiang P, Murray JJ. Evaluation of NeuroBloc™ (Botulinum Toxin Type B) Efficacy in Patients with Cervical Dystonia. Abstract – International Conference 1999: Basic and Therapeutic Aspects of Botulinum and Tetanus Toxins, Orlando, FL, 1999 (in press).

Bever CT, Vollmer TL, Sheremata WA, **Koller M**, Hulme AJ, Wallcke PA. Inter-rater Variability in the Scoring of the Scripps Neurological Rating Scale (SNRS) and Expanded Disability Status Score (EDSS): Improvement with Training. Abstract - American Academy of Neurology Annual Meeting, Minneapolis, MN, 1998.

Sheremata WA, Vollmer TL, Stone LA, Willmer-Hulme AJ and **Koller M**. A Placebo-Controlled, Safety, Tolerability, Dose Escalation, PK Study of Various Doses of Intravenous Antegren® in Patients with Multiple Sclerosis (MS). Abstract - American Academy of Neurology Annual Meeting, Minneapolis, MN, 1998.

Truong DD, Cullis P, O'Brien C, **Koller M**, Garces A and Wallace J.: BotB™ (Botulinum Toxin Type B) is Safe and Effective in Botulinum Toxin Type A Resistant Cervical Dystonia Patients. Abstract - International Conference on Botulinum Toxin Munich, Germany. *Movement Dis* 1995;10(3):394.

Koller M for the American BotB Cervical Dystonia (ABCD) Study Group: BotB (Botulinum Toxin Type B) in the Treatment of Cervical Dystonia (CD) - Protocol AN072-008: An Interim Analysis. Abstract - International Conference on Botulinum Toxin Munich, Germany. *Movement Dis* 1995;10(3):372.

Koller M. and Engel W.K.: Increased Serum Creatinine Kinase MB Isozymes (CK-MB) and Alkaline Phosphatase Positive (AP+) Regenerative Muscle Fibers in Amyotrophic Lateral Sclerosis (ALS). *Neurol* 1984;34(supp 1-March):81.

BOOK CHAPTERS:

Cullis PA, O'Brien CF, Troung DD, **Koller M**, Villegas TP and Wallace JD. Botulinum Toxin Type B: An open label, dose escalation, safety and preliminary efficacy study in cervical dystonia patients. *Dystonia 3 Advances in Neurology*, Vol. 78 (Chapter 23), p. 227-230, edited by S. Fahn, CD Marsden and M DeLong. Lippincott-Raven Publishers, Philadelphia, 1998.

MISCELLANEOUS:

Physician Sponsored - I.N.D. - Research Protocol: Etiocholanolone Protocol evaluating its potential use in the treatment of chronic relapsing polyneuropathies v. Poly-ICLC therapy. 1983.

Koller M. Land Utilizations and Community Health. Master's Thesis. University of Texas at Houston, School of Public Health. August 1973.

Koller M. An Analysis of the Metabolic Function of the Avian Glycogen Body. Indedpendent Research Program, Franklin and Marshall College, June 1972.

Glasser B and **Koller M.** The Effects of Insulin upon the Oxidative Respiration of the Avian Glycogen Body. Independent Research Program, Franklin and Marshall College, June 1971.

References Available Upon Request

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